The summarydiagram of discovered host immunological pathways against different pathogens and its relation to hypersensitivities

Running title: summary diagram of host immunities

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Abstract
Background: Since Professor Mosmann proposed TH1 and TH2 immune reactions. Recently, more host immunological pathways are discovered including TH17, TH9, TH22, Tr1, Treg, Tfh, TH3, and TH1like. These immunological pathways' functional clinical importance is not clearly known. In this article, the host immunological pathways are re-organized to get a clear picture. Main text: There are four eradicable immune responses: TH1/TH2/TH22/THαβ which are corresponding to four tolerable immune responses: TH1Like/TH9/TH17/TH3. TH1/TH1like is immunity against intracellular bacteria or protozoa and is related to type4 delayed-type hypersensitivity. TH1 immunity includes M1 macrophage, CTL(Tc1/EM4), IFNg CD4 T cell, and IgG3 B cells. TH1Like immunity includes M2 macrophage, suppressive CTL(EM3), IFNg/TGFβ CD4 T cell, and IgA1 B cells. TH2/TH9 is immunity against helminthes and is related to type1 immediate allergy. TH2 immunity includes eosinophils(iEOS), basophil/mast cells(MCct), IL-4 CD4 T cells, and IgE/IgG4 B cells. TH9 immunity includes eosinophils (rEOS), basophils/mast cells(MCt), IL-9 CD4 T cells, and IgA2 B cells. TH22/TH17 is immunity against extracellular bacteria or fungi and is related to type3 immune-complex hypersensitivity. TH22 immunity includes neutrophils(N1), IL-22 CD4 T cells, and IgG2 B cells. TH17 immunity include neutrophils(N2), IL-17 CD4 T cells, and IgA2 B cells. THαβ/TH3 is immunity against viruses and is related to type2 antibody dependent cytotoxic hypersensitivity. THαβ immunity includes stimulatory NK cells(NK1), CTL(Tc2/EM1), IL-10 CD4 T cells, and IgG1 B cells. TH3 immunity includes regulatory NK cells(NK2), suppressive CTL(EM2), IL-10/TGFβ CD4 T cells, and IgA1 B cells. THfh is the stimulatory pathway to initiate adaptive immunity. Cytokines can help to drive initiatory immunities to eradicable immune reactions. Another inhibitory pathway Treg is the key player to shift immune

responses to tolerable immune responses for generating milder cytokines and other immune mediators to avoid severe destruction of tissue-organ during chronic large scale infection. Conclusion: This 4x2+2 is the whole diagram of host immunological pathways describing initiatory, eradicable, regulatory, and tolerable immune responses.

Key words: TH1, TH2, TH3, TH17, TH22, THfh, Treg, TH9, TH1like and Tr1(THαβ)

Background

There are many discovered host immunological pathways including traditional TH1, TH2, TH3, TH17, TH22, THfh, Treg, TH9, and Tr1(THαβ). These identified pathways are not logically organized. Here, I will propose a detailed picture about the whole context of host immunological pathways. (Figure 1)

The traditional TH1/TH2 paradigm was proposed by Dr. Mosmann in 1986.(56) TH1 was thought the host immunity against viruses and intracellular bacteria. TH2 is the host immunity against multicellular parasites (helminthes). In my PhD thesis, I proposed a new THαβ immunological pathway against viruses that is divided from traditional TH1 immunity.(36) The TH1 immunity is then focusing on intracellular bacteria and protozoa. Then, TH3 immunity and Tr1 immunological pathways were identified later.(44,45) Recently, additional immune responses are discovered including TH17, TH22, THfh, Treg, and TH1-like immunological pathways.(13,20,22,31,35)

Main text

Initiatory immune response

Follicular helper T cells (THfh) is thought to be the key helper cells for the B cell germinal centers in lymph nodes.(84) THfh cells are characterized by IL-21 producing T cells(23,50). BCL6 is a key transcription factor for THfh. TGF beta with STAT5 signal can constrain the differentiation of the IL-21 producing helper T cells(49,52). IL-21 production is also related to STAT1and STAT3 activation as well as STAT5 activation. Since immunosuppressive prolactin can induce STAT5a to suppress BCL6 expression.(40,78)On the contrary, STAT5b can up-regulate BCL6.(73)STAT5a and STAT5b have distinct target genes in immune responses.(82)The transcription factor to induce THfh should be STAT5b. BCL6 is key in THfh development.(7,47,61)Follicular helper T cell can induce B cells to start to produce IgM antibody.(9) Thus, it is the

earliest T lymphocytes to begin the adaptive host immunity.(12,59,72) Different STAT proteins regulate different immunological pathways.(51,74) If the infection is tend to be eradicable, the following host immunological pathways are generated with other cytokines.

Eradicable immune responses

TH1 immunity is driven by IL-12. It is the host immunity against intracellular bacteria or protozoa. The main effector cells of TH1 immunity are stimulatory macrophages (M1), IFNg secreting cytotoxic CD8 T cells (EM4 CD27-CD28+ Tc1), IFNg secreting CD4 T cells, and IgG3 producing B cells.(3,28,38,70)The key transcription factors for TH1 immunity is STAT4. T-bet also plays a vital role in TH1 immunological pathway. TH1 immunity against self antigen is Type 4 Delayed-type hypersensitivity such as type1 diabetes mellitus.(41,55)

TH2 immunity is driven by IL-4. TH2 immunity is against extracellular parasites (helminthes). The main effector cells of TH2 immunity are eosinophils (iEOS), basophils/connective tissue mast cells(MCtc, mast cell tryptase & chymase), IL-4/IL-5 secreting CD4 T cells, and IgG4/IgE producing B cells.(53)IgG4 activates eosinophils and IgE activates mast cells such as in acute anaphylaxis, respectively.(77) The key transcription factor for TH2 immunity is STAT6. GATA3 also plays a vital role in TH2 immunological pathway. TH2 immunity against self antigen is Type1 immediate allergy such as food/drug allergy or urticaria.(34)

THαβ is distinguished from the traditional TH1 immunity(36). THαβ immunity is against viruses. It was called Tr1 cell by some previous researchers.(45)THαβimmunity is driven by IFNa/b or IL-10. The main effector cells of THαβ immunity are IL-10 producing stimulatory NK cells(CD56-CD16+ NK1 cells), IL-10/IL-27 secreting CD4 T cells, IL-10 secreting cytotoxic CD8 T cells (EM1 CD27+CD28+ Tc2), and IgG1 producing B cells.(15,38,41,67,70)CD27 molecule is important for virus immunity.(33,58)The key transcription factor for THαβ immunity is STAT1and STAT2.(60)THαβ immunity against self antigen is Type 2 Antibody dependent cytotoxic hypersensitivity such as acute stage of Myasthenia Gravis. It is worth noting that IL-10 is not merely a immunosuppressive cytokine; it can have potent stimulatory effects on NK cells, CTLs, and B cells.(57)

TH22 is the host innate immunity against extracellular bacteria and fungi(2,88). TH22 is driven by IL-6 or TNFa(26,79). The main effector cells for TH22 immunity are

PMNs(N1), IL-22 secreting CD4 T cells, complements, pentraxins, and IgG2 producing B cells.(21,22)The key transcription factor for TH22 is STAT3(90). AP1 and CEBP are also important. TGF beta can suppress IL-22 to skew to TH17 immunity.(71)TH22 against self antigen is Type 3 immune-complex and complement mediated hypersensitivity such as Arthus reaction.(92)

It is interesting to know that four IgG subtypes fit the four types of acute immunological pathways. Murine IgG antibodies also have four subclasses. There is a correlation between murine and human IgG subtypes: Human IgG1<->Murine IgG2a; Human IgG2<->Murine IgG3; Human IgG3<->Murine IgG2b; Human IgG4<->Murine IgG1.(37) hIgG1/mIgG2a is against viral antigens; hIgG2/mIgG3 is against bacterial antigen, especially polysaccharides; hIgG3/mIgG2b is against intracellular bacteria; and hIgG4/mIgG1 is related to parasite antigens.(17,27,75,81)

Regulatory immune responses

Treg is the host immune inhibitory mechanism(35). It is driven by IL-2 and TGF beta. The main effector cells for Treg are TGFb producing CD4 T cell and IgA producing B cell. The key transcription factor for Treg pathway is STAT5, especially STAT5a. But, both STAT5a and STAT5b play non-redundant roles in Treg generation.(89) They may act sequentially with STAT5b activation first in THfh signaling. Combined STAT5b and STAT5a signaling induces the generation of Treg. The combination of Treg and the above four immunological pathways is important to shift adaptive immunity to tolerable immunity. During the initial infection, acute stage fierce cytokines can rapidly kill pathogens as well as infected cells or tissues. However, if the pathogen infects a lot of cells in a tissue such as liver, to kill the infected cells will total destroyed the organ.(86) Thus, regulatory T cells STAT5 signal combining TH1/TH2/TH22/THαβ will make CD4 T cells with less fierce cytokines.(89) Then, TH1like/TH9/TH17/TH3 immunological pathways will be generated in more chronic stage. It is worth noting that there are two subtypes of IgA antibodies: IgA1 and IgA2. IgA1 is the dominant IgA antibody in serum, and IgA2 is the dominant IgA in mucosa. TGF beta can induce either IgA1 or IgA2 which seems to be dependent on lymphoid follicle location.(91) In GULTs or Peyer's Patch, IgA2 is the dominant IgA antibody produced in GI mucosa there. In lymph nodes of other body locations, IgA1 is the dominant IgA antibody produced there.(1) However, IgA1 is especially related to viral protein antigens and IgA2 is especially related to bacterial antigens such as LPS.(32) The heavy chain locus sequence of B cell antibodies is IgM, IgD, IgG3, IgG1, IgA1, IgG2, IgG4, IgE, and IgA2. First, B cells double express IgM and IgD. We can view IgG3,

IgG1, and IgA1 as the first group for cellular immunity. Then, IgG2, IgG4, IgE, and IgA2 can be viewed as the second group for humoral immunity. The gene sequence order is important, and it affects the time sequence of isotype switch. It is also worth noting that IL-13 is also a Treg related cytokine which is pro-fibrogenic and related to TGF beta signaling.(64,83)

Tolerable immune responses

TH1-like cells (non-classic TH1) are initiated by TGF beta(STAT5 signaling) and IFNg(STAT4 signaling). TH1-like cells with Foxp3+ regulatory character are identified.(20,62)There is a close relation to TH1 helper cells and TH1-like cells.(65,69)TH1-like cells are the chronic host immunity of TH1 immune response. Thus, it could be related to chronic inflammation such as long-term tuberculosis infection. The effector cells of TH1-like immunity include suppressive macrophages (M2), suppressive CD8 T cells (EM3 CD27-CD28-), IgA1 producing B cells, and IFNg/TGFb producing CD4 T cells.(5,28,29,70)TH1-like immunity induces type4 delayed-type hypersensitivity such as Crohn's disease.(16)

TH9 cell is driven by IL-4 (STAT6 signaling) combining TGF beta(STAT5 signaling).(18,25,30)Thus, TH9 cell is closely related to TH2 immunological pathway. It is characterized by IL-9 secreting CD4 T cell. TH9 cells are found to be important in chronic allergic condition such as asthma. Thus, TH9 helper cell is the chronic T helper cells related to TH2 immunity. The effector cells of TH9 immunity include regulatory eosinophils(rEOS), basophils/mucosal mast cells (MCt, mast cell tryptase), IL-9 producing CD4 T cells, and IgA2 producing B cells.(87) TH9 immunity induces type1 allergy including asthma.(6,39,42,53,63,68,76)

TH17 cell is driven by IL-6 / IL-1 combining TGF beta(14,31). Thus, TH17 cell is closely related to TH22 immunological pathway. It is characterized by IL-17 secreting CD4 T cell. TH17 cells are found to be important in chronic immune-complex mediated disease such as rheumatic arthritis. Then, TH17 helper cell is the chronic T helper cell related to TH22 immunity.(46)TGF beta with STAT5 can suppress the acute IL-22 producing cells and enhance the chronic IL-17 producing cells(48,71). Because of the role of TGF beta in TH17 immunity, regulatory IL-17 producing cells are noted.(8,85) The effector cells of TH17 immunity include regulatory neutrophils(N2), IL-17 producing CD4 T cells, and IgA2 producing B cells.(24,32)TH17 immunity induces type3 immune-complex hypersensitivity including ulcerative colitis.(4,54)

TH3 cells are driven by IL-10 and TGF beta.(11,19)Thus, TH3 cells are closely related to THαβ immunological pathway. It also produces IL-10 as well as TGF beta. Thus, TH3 helper cell is important to chronic antibody dependent cellular cytotoxic hypersensitivity. TH3 cell is the chronic helper T cells corresponding to THαβ helper cell. The TH3 immune effector cells include IL-13 producing regulatory NK cells(CD56+CD16- NK2 cells), IL-10 and TGF beta secreting CD4 T cells, suppressive CD8 T cells (EM2 CD27+CD28-), and IgA1 producing B cells.(43,67,70,80) IgA1 is produced in serum and is against viral protein antigens. TH3 immunity induces type2antibody dependent cytotoxic hypersensitivity including chronic stage of SLE.(10,66)

Conclusions

This summary diagram: 4x2+2 immunological pathways are the whole pictures of host immunological pathways. There are four eradicable immune responses: TH1/TH2/TH22/THαβ which are corresponding to four tolerable immune responses: TH1Like/TH9/TH17/TH3. It will match the four types of hypersensitivity. Then, we can clearly understand the detailed immune response against different pathogens as well as allergy/hypersensitivity.

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Wan-Chung Hu is completely responsible for the idea formation, literature research, and manuscript writing for this review study.

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The author declares that he has no competing interests.

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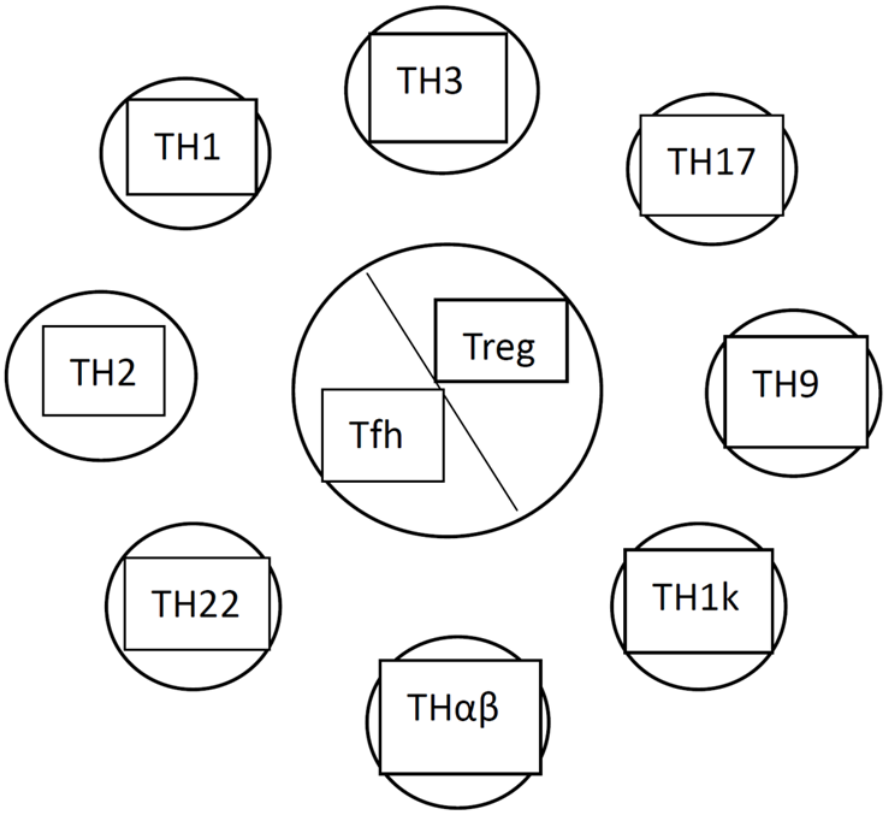
Figure legends

Figure 1. The summary diagram of host immunological pathways. In the middle, Tfh side (follicular help T cell) begins the initiatory immunity; on the other hand, Treg side (regulatory T cells) starts the regulatory immunity. Eradicable TH1 and tolerable TH1-like(TH1k) are related in the diagonal line. Eradicable TH2 and tolerable TH9 are related in the diagonal line. Eradicable TH22 and tolerable TH17 are related in the diagonal line. Eradicable THαβ and tolerable TH3 are related in the diagonal line.


TH3
TH1
TH17
TH2
Treg
Tfh
TH9
TH22
TH1k
THαβ